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STATISTICAL STUDIES IN IMMUNITY.

SMALLPOX AND VACCINATION.

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In writing this paper on smallpox and vaccination I have no intention of entering into any controversy upon the subject. The fact that vaccination protects against smallpox is assumed, and consideration is alone given here to the relationship between vaccination, revaccination, and smallpox, in so far as the facts throw light upon the growth, decline, or establishment of immunity in persons who have passed through one or other of these infections. I would rather have chosen for this investigation some other disease, but as an inquiry of this kind is essentially statistical there was no other series of figures available. The disadvantage of choosing vaccination and smallpox arises from the fact that the former is to a considerable extent different from the latter, and though there seems good reason for believing that vaccination is a disease caused by the parasite of smallpox so modified as to have lost one stage in its life history, yet the fact that it protects chiefly against the second stage of smallpox causes the immunity relationship to be of a more complex character than is desirable.

Before proceeding, however, to consider the relationship of smallpox to vaccination one fact demands special preliminary notice: that is the change which has taken place in the age at which vaccinated persons are attacked by smallpox. All over the country from the earliest period of last century for which statistics are available there has been a steady increase in the mean age at which such persons have been attacked by smallpox.

This is quite distinct from the rise in the mean age at death, shown by the combined mortality statistics of the vaccinated and unvaccinated which is commonly and correctly looked upon as largely due to the protective influence of vaccination upon the younger members of the community. What I refer to is a process which applies specially to the vaccinated, and which does not seem to admit of any complete explanation from the point of view of alteration in the character of the population. In London, for instance, between the years 1836

and 1851, of 3,094 cases 2,719 were under the age of thirty, or more than seven vaccinated persons under thirty were affected with smallpox for each individual above that age. In Dr Gayton's statistics relating to the period 1870 to 1883 the corresponding proportion is 5½ to 1. In Dr Sweeting's referring to 1880 to 1885 the proportion is 3 to 1, while in the epidemics of the last ten years two

TABLE I.

Age of Smallpox Attack in Case of Vaccination.

Age Periods	London, 1836–51		London, 1870–72		London, 1880–85		London, 1892–95		London, 1902	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
0—5	7	2	195	38	26	—	15	—	16	—
5—10	56	7	786	60	108	2	101	—	98	2
10—15	206	10	4504	238	256	8	188	2	265	3
15—20	866	49			405	10	533	5	654	17
20—25	1058	93	3761	410	632	59	639	16	1049	45
25—30	526	55					454	16	1017	70
30—35	210	21	1297	257	455	68	370	14	827	91
35—40	102	20					234	14	616	111
40—50	61	10	435	110			293	8	726	154
50—60	2	1	134	30			89	8	254	52
60—70	—	—	62	12			24	7	105	27
70—							10	1	36	6
0—30	2719	216	9246	756	1427	79	1950	39	3099	137
30—	375	52	1928	389	455	68	1020	52	2564	441
Mean Age	22·6	24·5	21·9	26·4			26·4	33·4	28·6	38·2

persons under thirty years only are affected for each one over that age. In every town where there are statistics for a series of outbreaks of smallpox during the last thirty years exactly the same fact is observed. To mention Glasgow; in 1872 this proportion was 6 to 1, in 1892 to 1895 2½ to 1, and during the epidemic of 1901 the ratio reached unity. Now there can be no doubt that a part of this is due to the gradual disappearance of adult persons protected by previous attacks of smallpox. In addition during the years immediately succeeding Jenner's discovery vaccination was performed promiscuously on young and old alike, and persons vaccinated in adult years must have constituted during the first sixty years of the century a very considerable proportion of the total vaccinated persons at higher ages, as it can easily be seen that any person in 1836 whose age was greater than thirty-seven must have been vaccinated at the earliest at an age corresponding to the difference of the actual age and of thirty-seven years. By 1870, however, both these influences must have to a considerable extent disappeared, and yet we see that the change referred to has been going on just as markedly since that date. Against these two factors must be set one which undoubtedly acts in the opposite direction, and that is the gradual better enforcement of vaccination during infancy, which, by continually providing a larger number of vaccinated persons at lower ages, ought if no other change were taking place to supply a greater number of cases at these ages. The influence of this should at least be sufficient, at any rate since 1870, to neutralise that due

to the factors before mentioned. Unfortunately there is a complete absence of statistics referring to this matter, so that an examination of the relative influences of these different factors is impossible. The effect of revaccination on the age incidence of persons suffering from smallpox can be more readily estimated. When performed in the absence of an epidemic, or when slight outbreaks only of this disease are present, there is not a sufficient amount done to influence statistics much one way or another. In Sheffield, for instance, when the great epidemic of 1887 occurred, about five to seven per cent. of the population at each age period above fifteen years were found to be revaccinated. When, however, as in this epidemic in Sheffield and in the late epidemics in Glasgow revaccination is performed on a large scale, it is found that a much larger proportion of persons between ten and twenty years of age avail themselves of this means of protection than at higher ages. The effects of this on later epidemics are obviously, (1), if the second epidemic occurs within a few years of the first to raise the mean age; and (2), if the later epidemic occur about fifteen years thereafter to lower the mean age of attack. Revaccination, however, as a rule only begins to have an important modifying effect on the epidemic concerned when it is naturally approaching its end.

The change in the age incidence of smallpox just discussed is one which not only applies to the vaccinated as a class, but equally to the different groups comprehended in this class. Persons suffering from smallpox are for the purpose of classification commonly divided into groups as they present on their arms one, two, three, and four or more vaccinal cicatrices. In each of these groups the mean age has steadily risen. Now with regard to the group of those who present one cicatrix this is to be expected. Since 1870 persons vaccinated in this manner have been becoming progressively fewer and fewer, and consequently in London the bulk of those presenting one vaccinal cicatrix must consist of persons at the higher ages. Exactly the same change in the mean age, however, is found to be among the members of the group presenting one cicatrix in Glasgow, although no such change in the method of vaccination has taken place there. With regard to the group, however, of persons with four or more scars, year by year since 1870 a larger and larger number of such have come into existence at lower ages and consequently it would be expected that the mean age among this group would be at any rate stationary if not lower. This is not found to be the case. The annexed table exhibits the change in the mean age which has taken place in London since 1870. The rise noted in the mean age of persons with four marks

TABLE II.

Mean Age of Cases and Deaths in the Epidemics in London, 1870—1902.

	One Scar		Two Scars		Three Scars		Four Scars	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1870–83	21·8	26·2	21·0	25·1	18·1	24·0	17·0	24·8
1892–95	26·8	35·3	29·5	43·9	26·5	31·7	23·2	35·7
1902	34·2	39·6	34·0	41·3	31·0	37·7	27·2	34·5

in view of the fact just mentioned seems to establish that this phenomenon is not due to alteration in the character of the population, but presents a biological as distinct from a statistical change. The explanations which can be offered from the biological point of view are three. Firstly, there may be some secular change taking place in the susceptibility of the population towards smallpox itself; secondly, there may be a like change taking place in the smallpox organism; and thirdly, it is possible that the passage of the organism of vaccinia through several thousand generations in the human subject has gradually increased the protective value of lymph; here again, however, there may be secular change. This increase in protective value, while it cannot be held proved, is in striking contradiction to what has been hitherto considered as probable. Plants propagated by cuttings, by tubers, and such like means, are well known to deteriorate in quality, and frequent recourse must be had to propagation by seeds if the strength of the species is to be maintained. To this rule, however, there are certain exceptions. Though it cannot be distinctly averred, however, that the vaccinal lymph has increased in potency, it can with all certainty be maintained that there is no evidence in favour of its deterioration. The evidence on which the argument regarding the deterioration of lymph was based cannot be regarded as complete. The chief points were, firstly, that as the century went on it became increasingly more possible to revaccinate successfully; and secondly, that in making attenuated forms of sheep-pox corresponding, as was thought, to vaccination, it was found that after a few generations these could not be relied on to give protection. In view of our fuller knowledge of the probable life history of the smallpox organism and its relations to vaccinia this latter argument ceases to present a reasonable analogy, while the former is more explicable on the view of the increasing potency of the lymph than on the other hypothesis.

The change just described is one which affects vaccinated persons as a whole and bears no special relationship to the question of the growth and decay of immunity. It is then to be noted that in all further discussions of smallpox statistics throughout the course of this paper the comparisons which are drawn, as far as possible concern persons in the same epidemic in the same place, because with different age constants at different places and at different times it can be seen what contradictory inferences could be made.

The first fact with regard to the immunity conferred by vaccination is one which seems unexpected. It is found that persons who are well protected have for all epidemics at all places a lower mean age than those who are badly protected. Exactly the same remarks apply to the groups which are based on the size or character of the cicatrix. Thus in each epidemic persons with four good marks have a lower mean age than those with four indifferent marks, a relationship which also applies to the group of persons presenting one, two, or three cicatrices. Taking the statistics of the large epidemics in Glasgow, of which more than half the cases consist of persons with one mark, it is found that the mean age in each of the three outbreaks falls steadily as the size of the mark

increases; that this is not due merely to the fact that larger marks are now put on than were formerly is shown moderately conclusively when it is considered further in detail. The degree of foveation of a cicatrix has been regarded as an indication of its protective value. Foveation, as a result of vaccination, no

TABLE III.

Mean Age of Persons with one Scar of different sizes, Glasgow 1901, 1902, *and* 1904.

Size of Scar	1901		1902*	1904
	Foveated	Not Foveated		
0—·25 sq. in.	32·7	33·7	38·3	37·3
·25—·5 „	31·6	32·1	34·8	33·3
·5—1 „	28·1	29·3	33·4	32·0
1— „	26·1	27·5	28·3	32·9

physician can foretell. The number, and, to a certain extent, the size of the cicatrices, is in the hands of the operator, but as to whether the scar will turn out to be foveated or not depends upon a number of factors beyond his control, and yet the mean age of those with unfoveated scars is for each group higher than that of those in which the scars are foveated. This relationship also applies uniformly as far as I have been able to observe, and in the large epidemics where there is a sufficient number of cases to allow of finer gradation the same relationship holds. For instance, taking those cases in the epidemic in London in 1902 in which there are four cicatrices of collective area greater than $\frac{1}{2}$ square inch it is found that among those in which more than half of this area is foveated the mean age is lower than that of those in whom less than half is foveated, and that the mean age of the latter is in defect of that of those patients in whom there is no foveation, the cicatrix being glazed or puckered. I do not think that this can be explained as may be suggested on the ground that foveation is a feature of the scar which tends to disappear with age, for it must be noted that the relationship just described bears a constantly present inverse proportion to that observed to exist between the same subdivisions and the mortality: that is to say, many marks are a better protection against death than few, larger than smaller, and foveated than non-foveated, and this to a greater extent than the mere difference of age incidence would imply.

The susceptibility to smallpox of those with different numbers of marks is unfortunately a matter which cannot be determined directly, and consequently its full significance cannot be expressed in figures. It however can be investigated for London to a certain extent. At intervals of ten years since 1870 large outbreaks of smallpox have occurred in London. The number of persons affected at each age period with the number of their vaccinal scars is therefore known at four epochs separated by almost equal intervals of time, and consequently the way

* The incidence of mean age is here due to the fact that the revaccination in 1901 was performed more largely in the earlier than in the later ages.

in which persons are protected by different kinds of vaccination can be judged by a comparison of the proportions in each group at the same age period at the different epochs. Persons thus of the age five to ten years in 1872 will be fifteen to twenty in 1882, and will be thirty-five to forty-five in 1902. These proportions are recorded in the accompanying table. From this it may be seen that in general after forty years all vaccinated persons are apparently equally liable to smallpox. The proportions of persons attacked with smallpox who were from forty to sixty in 1872, sixty to eighty in 1892, and above seventy in 1902 with one, two, three, and four scars respectively, are sensibly constant considering the small number of

TABLE IV.

Table showing the Percentage of Persons attacked by Smallpox, with the different numbers of Vaccinal Cicatrices at each age period, in the Epidemics 1870—72, 1880—85, 1892—95, *and* 1902 *in London.*

Group I. Persons 0—10 years, 1870—72.

Epidemic	Age Periods	One Scar	Two Scars	Three Scars	Four Scars
1870—72	0—10	24·6	25·5	22·6	27·3
1880—85	10—20	20·7	25·7	31·3	22·2
1892—95	20—30	14·3	23·7	28·3	35·1
1902	30—40	7·9	14·2	24·8	51·1

Group II. Persons 10—20 years, 1870—72.

Epidemic	Age Periods	One Scar	Two Scars	Three Scars	Four Scars
1870—72	10—20	22·2	36·8	23·3	17·5
1880—85	20—30	21·3	32·3	26·0	19·9
1892—95	30—40	20	27·0	29·0	23
1902	40—50	18·4	28·4	27·1	25·9

Group III. Persons 20—30 years, 1870—72.

Epidemic	Age Periods	One Scar	Two Scars	Three Scars	Four Scars
1870—72	20—30	24·6	39·6	19·4	16·7
1880—85	30—40	—	—	—	—
1892—95	40—50	28·6	28·4	15	22·8
1902	50—60	16·7	35·6	23	22·5

Group IV. Persons 30—40 years, 1870—72.

Epidemic	Age Periods	One Scar	Two Scars	Three Scars	Four Scars
1870—72	30—40	29·8	41·6	17·8	16·6
1880—85	40—50	—	—	—	—
1892—95	50—60	24·7	30·3	21·3	23·6
1902	60—70	26·4	31·8	18·7	23·1

Group V. Persons 40—60 years, 1870—72.

Epidemic	Age Periods	One Scar	Two Scars	Three Scars	Four Scars
1870—72	40—60	32·7	39·1	16·6	10·4
1880—85	50—70	—	—	—	—
1892—95	60—80	50	32·3	5·9	11·8
1902	70—	39·9	37·1	11·2	11·2

attacks at these ages. Persons with four marks are relatively well protected under five years, which is to a certain extent explained on the ground that the bulk of the patients at that age period belong to the class with very imperfect marks. Between twenty and forty years the advantage seems greatest, and after forty it has apparently entirely disappeared. Exactly the opposite would appear to be the case with persons with one mark. The cause of this in the early years, however, has just been explained, and the apparent decrease in later years is accounted for largely by the fact that a steady equalisation of susceptibility among the four groups takes place, and the number of persons with several cicatrices increases in proportion. It is to be noted that it is apparently between twenty and forty that persons with four scars have most advantage over persons with one. It may be added that the group of those with three marks resembles in general that with four, and the group with two that with one. This question of relative susceptibility at different ages is closely allied to that just discussed regarding the lowering of the mean age in those groups where vaccination is most perfectly performed. It certainly cannot be inferred from the latter that the more incomplete the vaccinal protection the more likely is the attack of smallpox to be delayed, provided such an attack is going to come. It appears much more likely that the decay of protective power is longer delayed, and that consequently while for the first twenty years or so any kind of fair mark indicates much the same protective power, there is a period in the middle ages of life when those who have good cicatrices are much better protected than those with inferior, and again after this period of relative protection has decayed all again become equally susceptible*. The only statistics which are available to check this conclusion are those of Warrington in the epidemic 1892–3, where a census as to the state of

* How this produces a higher mean age among those badly vaccinated than among those well vaccinated can be seen if the figures of Table V. are examined, though it is perhaps not immediately apparent. Here the divisions do not lend themselves to any accurate calculation of mean ages. In the approximations however the mean age of all those found to be badly vaccinated is in much the same excess over that of all found to be well vaccinated, as the mean age of those in the former class who were attacked is in excess of the mean age of those in the latter. But this high mean age among the badly vaccinated attacked by smallpox is not necessarily a consequence of this grouping of the population in the houses invaded by smallpox. As high ages are more susceptible among the badly vaccinated the population of the houses invaded will necessarily contain more old persons as there must be some correlation of age among persons living in the same houses, young families being of course more common among young parents. The high mean age referred to is independent of this, as will be seen if the percentage attacks in both are calculated. These show that in equal populations the mean age of those badly vaccinated attacked by smallpox would be in considerable excess of that of the well vaccinated.

Proportions Attacked.

Age Periods	Well Vaccinated	Badly Vaccinated
0—10	3·7	6·8
10—20	22·6	19·5
20—30	48·3	47·1
30—40	27·5	54·9
40—50	16·2	19·7
50—	13·4	19·5

vaccination was taken for the different age periods of all those in infected houses. Unfortunately the vaccinal scars are simply divided into two classes according as they exhibit good or imperfect characters. It will be seen that under ten years those well vaccinated have a certain measure of protection probably for the reason

TABLE V.

Correlation between Exposed and Attacked, Vaccinated Well and Badly, Warrington, 1893.

	Well Vaccinated			Badly Vaccinated			
Age Periods	Not Attacked	Attacked	A·R	Not Attacked	Attacked	A·R	Correlation
0—10	466	18	3·9	124	9	6·7	+·21
10—20	346	114	25·3	136	32	19·1	−·13
20—30	144	135	48·3	74	66	47·1	−·03
30—40	95	36	27·5	46	56	54·7	+·43
40—50	98	19	16·2	61	15	19·8	+·09
50—	45	7	13·4	68	14	17·1	+·14

already indicated, from ten to thirty years there is practically no difference between the classes. Between the ages of thirty and forty the advantage however is very definitely in favour of those with good marks, and after the age of forty this is still present, though not nearly so marked. These figures so far as they go confirm the explanation just given.

Before proceeding further to discuss the character of the immunity conferred by vaccination it is necessary to have as far as possible an accurate knowledge of the susceptibility to smallpox exhibited at different ages among persons who have no acquired protection at all either from vaccination or previous attack of the disease. With regard to the age susceptibility to smallpox in an unvaccinated community not a great deal can be said. In prevaccination days statistics were rarely kept with any accuracy, and though records of death in age periods exist relating to considerable numbers of persons and considerable periods of time, yet these afford a quite inadequate basis on which to compute the susceptibility at different ages. The most complete tables calculated from the number of deaths are those published by Duvillard with the authority of the French Academy of Sciences in 1806. He deduces the result that persons at all ages are about equally susceptible to smallpox, but that the maximum susceptibility is between the ages of ten and eleven years, though the excess is small. His conclusions lead him, however, into the difficulty of requiring that a much larger number of persons at a higher age should be attacked by smallpox than is actually observed. He explains this on the ground that the great majority of these attacks are so mild as to escape notice. Now of this there was no evidence at the time at which Duvillard wrote, nor is there any at the present date, when the diagnosis of modified smallpox has been brought to as great a pitch of perfection as any clinical diagnosis can. Consequently his conclusions afford an example of the untrustworthiness of calculating the susceptibility at different ages from the number of deaths alone without any knowledge of the actual case mortalities. For the determination of the susceptibility at different ages among persons who

are unvaccinated at the present day certain statistics exist. The chief of these are contained in the account of the epidemic in Sheffield in 1887 presented in Dr Barry's report to the Local Government Board. In this case a census was taken of nearly the whole population. The facts are tabulated so as to give the number of cases at each period who were unvaccinated, vaccinated, or revaccinated, and also those who had previously had smallpox. The state as regards the vaccination of the inhabitants of those houses actually invaded by smallpox is also tabulated separately. On account of the size of the epidemic this census must be held as the most important group of statistics at our disposal. It seems better to consider fully in the first instance the conclusions which may be based on these figures, and afterwards to compare the results with the statistics affecting naturally much smaller numbers which have been published with regard to other towns.

Considering, in the first place, the alterations in susceptibility to smallpox among the unvaccinated which takes place as the age increases, and expressing the relationship in terms of the correlation coefficients between those exposed to infection who escape, and those exposed who are attacked for each two succeeding age periods, it is found that these coefficients vary in the following

TABLE VI.

Correlation between those who were Attacked, and those who Escaped in Vaccinated and Unvaccinated respectively, at each age and that immediately succeeding.—Sheffield, 1887—8.

Age Periods	Vaccinated	Unvaccinated	Age Periods	Vaccinated	Age Periods	Unvaccinated
0— 1 & 1— 5	−·10	−·28	—	—	*0— 1 & 1— 5*	−·28
1— 5 & 5—10	−·21	−·17	—	—	*1— 5 & 5—10*	−·47
5—10 & 10—15	−·34	−·53	—	—	*5—10 & 10—15*	−·84
10—15 & 15—20	−·29	·72	—	—	*10—15 & 15—20*	−·20
15—20 & 20—25	·04	·04	*15—20 & 20—25*	·04	*15—20 & 20—25*	−·18
20—25 & 25—30	·01	·38	*20—25 & 25—30*	·04	*20—25 & 25—30*	·24
25—30 & 30—35	·09	·14	*25—30 & 30—35*	·13	*25—30 & 30—35*	·34
30—35 & 35—40	·26	·24	*30—35 & 35—40*	·31	*30—35 & 35—40*	·54
35—40 & 40—45	·47	·75	*35—40 & 40—45*	·53	*35—40 & 40—45*	·73
40—45 & 45—50	·48	−·25	*40—45 & 45—50*	·67	*40—45 & 45—50*	·47
45—50 & 50—55	·01	·80	*45—50 & 50—55*	·68	*45—50 & 50—55*	·95
50—55 & 55—60	·15	−·17	*50—55 & 55—60*	·77	*50—55 & 55—60*	·93
55—60 & 60—	·02	·04	*55—60 & 60—*	·79	*55—60 & 60—*	·92

way. From birth till between ten and fifteen years they are negative, indicating that the susceptibility steadily increases to this age, as was before found by Duvillard, and that thereafter each succeeding coefficient is positive of greater or less amount. If the susceptibility under one year is chosen for comparison with that of each succeeding age period it is seen that the strength of resistance which was less marked between ten and fifteen years has between twenty and thirty again increased so as to be equivalent to that in the first year of life, and thereafter steadily becomes greater. The period of maximum susceptibility between ten and fifteen years is one which is well marked in a large number of epidemics, although incapable of any very accurate measurement. The number

of children successfully vaccinated is published as a Government Return for every year since 1872, so that for epidemics occurring since 1890 for any definite place

TABLE VII.

Table showing the rate per Million of Attack by Smallpox among the Unvaccinated calculated as described in the text with the number of Attacks in an epidemic of Smallpox in 1726 *at Aynho in Northamptonshire for comparison.*

Age Periods	London, 1902	Leicester, 1892–93	Gloucester, 1895–96	Aynho, 1726
0— 5	—	255	727	13
5—10	315	607	909	15
10—15	543	700	955	33
15—20	584	554	774	14
20—25	339	396	434	16
25—30	225	386	446	9
30—35	150	77	351	32*

a rough approximation can be made of the respective number of vaccinated and unvaccinated, it being always borne in mind that the number of unvaccinated thus calculated is a maximum, and that many persons included have probably been vaccinated at some period subsequently during the existence of smallpox scares. The occurrence of such vaccination obviously becomes more probable the older the patient is, so that if a maximum is found between ten and fifteen years it is probably, as thus measured, to be in defect of the reality. The relative insusceptibility of old persons is also in statistics of epidemics an almost constant feature but the small numbers of unvaccinated persons attacked with smallpox from twenty years upwards makes the tracing of the development of insusceptibility in many cases less definite than in the case of Sheffield. This represents the main course of the increase and the decrease of susceptibility towards smallpox presented by the unvaccinated person. It is in general agreement with the few figures which exist regarding the age incidence of smallpox in the eighteenth century. This age incidence of course depends in a very large measure in any locality on the frequency with which epidemics occur. If epidemics break out every three or four years, as is known to have been the case in many places, then it is obvious that the most frequent age of attack will be that between two and three years, a characteristic well shown for example in the statistics of some German towns. The ages of two to three years indeed seem to constitute a period of greater relative susceptibility, as is already indicated in the figures for Sheffield, where the correlation coefficient between the age periods 0–1 and 1–5 years is greater than that between the periods of 1–5 and 5–10, though the numbers are too small to make this absolute. If, however, epidemics occur at greater intervals the natural period of greatest susceptibility will tend to become more evident. A maximum between ten and fifteen years is shown markedly in the statistics of Aynho in Northamptonshire, given by Dr Jurin, and, though in his record there is no statement to indicate the intervals between the succeeding epidemics, it is probable that this represents an epidemic outbreak of smallpox among a comparatively virgin community.

* This is number of cases above 30.

Still confining our consideration to the Sheffield figures we proceed to investigate the susceptibility among the vaccinated. Among these, as we pass from age period to age period an increase of susceptibility occurs from the period of vaccination till between the ages of fifteen to twenty years. At this age the period of greatest susceptibility is reached, and thereafter immunity is gradually regained, increasing with succeeding years, but never actually reaching that existing immediately after the operation was performed. It is to be noticed that the growth of immunity with old age proceeds from the age of twenty upwards in practically the same manner as among the unvaccinated. The curve is much more continuous, as is to be expected from the larger numbers which are available for its construction. The correlation coefficients fall slightly short of the similar ones for the unvaccinated, which is to be expected, as the old age protection starts originally from a higher level, the acquired immunity not being wholly lost at the age chosen for comparison. It is a matter of great interest from the point of view of the theory of immunity that with this large mass of statistics suitable for the calculation of the effect which one form of immunity produces upon another, namely, the effect of the presence of acquired immunity upon the growth of natural immunity, it is found that the latter develops exactly as if the former were completely absent. This is a result which could not have been anticipated, and its meaning will be further discussed in another paper.

The relative susceptibilities of the vaccinated and unvaccinated now falls to be examined, and here the Sheffield census is exceptionally valuable, as it allows the relative susceptibilities of vaccinated and unvaccinated to be determined and

TABLE VIII.

Table showing Correlation between Vaccinated and Unvaccinated Persons as regards Attack by Smallpox and escape from Attack when the numbers are considered of all persons (a) in the town itself, (b) in infected houses.

	(*a*) All persons in the town considered	(*b*) Those in the infected houses alone considered		
Age Periods	Sheffield, 1887–88	Sheffield, 1887–88	Dewsbury, 1892*	Leicester, 1892–93
0— 1	·84	·94	·90	1
1— 5	·63	·94	·93	1
5—10	·63	·96	·84	·93
10—15	·67	·99	·56	·77
15—20	·45	·72	·73	·50
20—25	·34	·74	·66	
25—30	·12	·40		
30—35	·17	·35	—	·17
35—40	·16	·39		
40—45	·11	·28	·30	
45—50	·19	·49		
50—55	– ·05	– ·11	– ·03	
55—60	·05	·07		
60—	·11	·05		

* In this instance the number of revaccinated persons and of those who have had previous attacks of smallpox are excluded in the statistics, so that the correlation coefficients are as free from error due to the admittance of such persons as is possible. The whole numbers affected are however small.

compared, not only when the risk of infection is comparatively slight, as in the general population, but when it is much more considerable, as in infected houses. In the annexed table are given in parallel columns a series of coefficients expressing the relative susceptibilities under each of these conditions for all age periods. It will be seen that the protection which vaccination affords against attack is much less strong, considered in relation to the total numbers of such persons in the town generally, than to the numbers in houses actually infected. In the former it ceases to be considerable after twenty-five years of age, and is practically negligible after the age of fifty. In infected houses, however, this decline is not nearly so marked, but after the age of fifty it also becomes practically negligible. This is an example of a property which at times seems to ensure a greater value to action on a mass than on a small section of that mass which differs from the mass in being apparently more vulnerable. It is not a case of the poison acting equally on the two classes as may be taken for granted is likely to be the case in invaded houses, but that the relative sparseness of unvaccinated persons affords them a protection beyond what random selection would give. It is conceivable that some such factor plays an adjuvant part in natural selection. There are no other statistics which enable comparison to be made between those in infected houses and those of the general population, but the relative susceptibility between the two classes of vaccinated and unvaccinated in infected houses has been calculated for some other epidemics, Leicester, etc., which show local differences, but exhibit on the whole the same kind of relation from age period to age period which has been noted in the case of Sheffield. All the figures agree in making a rapid fall in the protective power of vaccination after the age of fifteen years. It is, however, to be noticed that the protection against a severe attack of smallpox or death afforded by vaccination is of a much more permanent nature than that against an attack of the disease. This is to be expected when the clinical resemblance between vaccination and the second stage of the course of smallpox both as regards local appearances and the course of the pyrexia is recalled, and when it is noted that the clinical course of smallpox suggests the presence of two very different classes of toxins in the two different stages of the disease, so that the immunity against the first stage is much more readily lost than that against the second. That this is the explanation will be apparent when the close relationship between the protection against severe attack, that is an attack with a severe second stage of the fever, and a fatal attack is noted. There are no very ample data to determine this comparison, but in the annexed table will be seen in parallel columns the correlation betwixt recoveries and deaths, and mild cases and severe for the Gloucester epidemic of 1896, and it will be seen that the correspondence, considering the small numbers involved, is sufficiently close. The figures which Macdonell has already given are quoted for comparison, when it will be readily seen that the deaths give a very fair measure indeed of the severity of the disease, closer than might be expected when it is considered how large a factor the personal equation plays in the tabulation of degrees of severity. This is important, as the great majority of statistics

as published refer only to cases and deaths, and give no detail of the character of the illness.

TABLE IX.

Correlation, Vaccinated and Unvaccinated. Recoveries and Deaths, and Cases Mild and Severe, for Epidemic in Gloucester, 1896.

Age Periods	Recoveries and Deaths	Cases Mild and Severe
0— 5	—	—
5—10	—	·94
10—15	·94	·93
15—20	·77	·75
20—30	·63	·88
30—40	·73 } ·63	·68
40—50	·43 }	·63
50—60	} ·63	·60
60—	}	—

TABLE IX *bis.*

Correlation between Cases Mild and Severe and Recoveries and Deaths. Vaccinated and Unvaccinated (Macdonell).

	Recoveries and Deaths	Mild and Severe
Sheffield	·77	·79
Glasgow, 1892—5 ...	·78	·91
Glasgow, 1901 ...	·63	·51

The way in which the protection against death from smallpox afforded by vaccination is gradually lost is of considerable interest. As shown in the appended table it gradually decreases from the date of vaccination up to the age of twenty-

TABLE X.

Correlation, Vaccinated and Unvaccinated, Recoveries and Deaths in Various Epidemics.

Age Periods	London 1856–61	London 1870–72	Sheffield 1887	Gloucester 1896	London 1902
0— 5	—	—	1	1	1
5—10	·34	·74	·79	1	·77
10—15	·65 }	·60 }	·78	·94	·93
15—20	·59 }	}	·76	·77	·74
20—25	·66 }	·59 }	·67	·63 }	·61
25—30	·65 }	}	·49	}	·67
30—35	} ·70	} ·46	·55	}	·51
35—40	}	}	·53	·63	·43
40—45	} ·76	} ·31	·38	}	} ·74
45—50	}	}	·64	}	}
50—55	}	} ·42	·48	}	} ·65
55—60	}	}	} ·49	·62	}
60—65	}	}	}	}	} ·46
65—70	}	}	}	}	}

five, after which it is moderately constant. One point, however, of interest becomes manifest here, and that is the way in which the correlation coefficients for the different ages between vaccinated and unvaccinated tend to assume higher values, at the ages of 10 to 20 years*, as the century has gone on. Taking the first set of statistics which exist, namely those of Dr Marson, passing from these to the great epidemic of 1870–72 in London up to the last epidemic of 1902, we see the tendency for those coefficients to become larger continuously manifest, and the corresponding figures for the other epidemics for which they have been calculated seem to fit into place much as might be expected from their date of occurrence. This affords some confirmation of what has been suggested earlier in this paper in connection with the rise in age at which vaccinated persons are attacked with smallpox, namely, that vaccinal lymph has gradually gained potency through being passed for many generations through the human subject †.

The question now arises as to whether in different epidemics the extra protection which good scars are known to afford to their possessors compared with bad scars assumes greater relative importance in mild or severe epidemics. There seems, however, to be little difference. In the accompanying table will be seen

TABLE XI.

Correlation between Recoveries and Deaths in the Epidemics 1902 *and* 1892—95, *and* 1902 *and* 1870—83 *for each Vaccinal Group.*

Nature of Group	1902 & 1892–95	1902 & 1870–83
One Scar	·22	·43
Two Scars	·18	·37
Three Scars	·24	·43
Four Scars	·21	·52

the correlation between cases and deaths for the epidemic in 1902 and those in 1892–95 and 1870–83. These coefficients indicate that there is no great difference in a severe epidemic or in a mild between the manner in which each different group is affected in comparison with the same group in a severe or in a mild epidemic. The figures, it is true, show some little difference, but not much when it is considered that the change in the age distribution of the different groups has been proceeding not by any means equally in them all.

Another point which may be noted is the manner in which the relative protection against death between those with good and those with bad marks varies. It is found to differ not very considerably below the age of twenty, to

* The whole correlation coefficients are given in the table, but only the early years are referred to in the text, as adult primary vaccination was very common in the first half of the century.

† It is this change in the correlation coefficients which serves to differentiate the two interpretations which one puts on the rise of the mean age: (1) that due to the lymph gaining potency which is the cause of the rise of the general mean age of vaccinated persons attacked by smallpox, here the correlation between vaccinated and unvaccinated has increased as the century has gone on: and (2) the higher mean age of indifferently vaccinated persons taking smallpox than of well vaccinated, here the correlation between recoveries and deaths is in favour of the well vaccinated. It is thus seen that the mean age may be raised in two different ways. (Cf. footnote, p. 319.)

be at a maximum between twenty and thirty years, and then to gradually disappear towards old age. The figures here, however, are not large enough to base any definite conclusions.

It now falls to be considered at what rate immunity develops after vaccination, that is to say, how long must vaccination be performed prior to the onset of smallpox to prevent the attack? The incubation period of smallpox is from twelve to fourteen days, and it is found to be practically an absolute rule that no person develops smallpox more than fourteen days after a successful vaccination has been performed. If vaccination be performed during incubation period of smallpox the attack is seen often to be much modified. Here again the statistics refer to small numbers. In the first place, taking all ages together and estimating the correlation between the attacks and deaths in unvaccinated persons and in

TABLE XII.

Correlation between Recoveries and Deaths in Unvaccinated Persons, and those Vaccinated at various Dates prior to onset of illness.

Time before onset	Gloucester (all ages)	London (all ages)	London (ages above 1 year)
Days	1896	1902	1902
0— 3	·13	·06	·40
3— 6	·16	·12	·40
6— 9	·65	·47	·72
9—14	·14	·12	·45
14—	1·00	1·00	1·00

those vaccinated after infection, we find that even among those vaccinated within three days of the onset of the illness there is a distinct positive correlation in favour of the process. Among those vaccinated from three to six days before the onset of attack the correlation is slightly higher, from six to nine days it is very considerable, from nine to fourteen days, however, it is again very much less, apparently due to the fact, as will be shown later, that only a few persons who are really very susceptible develop the disease after nine days. After fourteen days the protection against death is absolute. If children under one year be eliminated from the numbers considered the protection is seen to be considerably higher, but still to exhibit a maximum at the period of six to nine days.

Though the subtraction of those cases under one year makes such a difference in the correlation coefficients, yet when those who have been vaccinated more than six days before the onset of the illness are compared for the varying age

TABLE XIII.

Correlation between Recoveries and Deaths of those Unvaccinated, and those Vaccinated 6—14 *days prior to onset of illness. London,* 1902.

Age Periods		
0— 1	·61	
1— 5	·63	
5—10	·73	·60
10—15	·38	
15—20	·49	
20—30	·61	

periods with those who are unvaccinated at the same age period it is found that the correlation is practically constant from birth onwards, and that the smaller correlation coefficients obtained when all ages are grouped together is brought about by the fact that a large proportion of the total cases are under one year, and that among these there is so special a mortality as to vitiate seriously the value of the correlation coefficients of the statistics when all ages are combined.

As to the actual susceptibility of persons vaccinated after exposure to smallpox there are no actual figures in existence. Some, however, can be inferred in the Gloucester epidemic; out of 653 persons vaccinated after exposure only 85 developed the disease as compared with 604 out of 832 among the unvaccinated who were exposed to infection and were not vaccinated. Out of the 85, 23 were vaccinated on the day of onset of the disease or on the day after, at a time when, therefore, the process could have no preventive action. The distribution of the remaining 62 persons is as follows: The number of those vaccinated from 0–3 days before the onset of attack was 19, from 3–6 days also 19, from 6–9 days 18, while for 9 days and upwards only 6. Now the great majority of persons exposed to infection are vaccinated within four days of the exposure, so that it becomes evident that if the operation be performed up to the ninth day before that on which onset of the attack could be expected there is a very high probability that no further developments will take place. This is a question on which statistics cannot be compiled, because, though a person may be exposed to infection for three to four days there is nothing to indicate on which day he may be infected, if at all, unless he subsequently develops the disease, so that the above figures are probably as satisfactory as any can be. The similar relation which exists between persons revaccinated more than six days before the onset of the

TABLE XIV.

Correlation between Recoveries and Deaths of those Vaccinated in Infancy only, and those Revaccinated 6—14 *days prior to onset of illness.*

Age Periods	London, 1902
20—40	·46
40—50	·35

illness shows a correlation of a similar kind, but not so great as in the former class, which is to be expected as before remarked, as the level of the protection from which the improvement is made is originally much higher. The smallness of the figures does not permit it to be given for more than two age groups.

The effect which an attack of smallpox exercises in establishing immunity is much more difficult to ascertain than that produced by vaccination. In general the great bulk of persons who are vaccinated have been vaccinated in infancy. With regard, however, to those who have had smallpox there are no data as to the ages at which they were attacked. In London between 1836 and 1851 out of 2654 unvaccinated persons suffering from smallpox treated in hospital only

690 were under the age of ten years; between 1870 and 1883 out of 2169 like persons 1197 were under the age of ten years. In both of these sets of statistics the distribution of the numbers from birth till ten years is fairly uniform. So that it may be taken for granted that towards the end of last century among persons over twenty years of age who had had smallpox previously one half was the greatest proportion of these who had the attack during the first ten years of life. In the accompanying table I have collected the details of fifty-one cases

TABLE XV.

Table of Second Attack of Smallpox.

Age at Second Attack.

Age at First Attack.	*15—20*	*20—25*	*25—30*	*30—35*	*35—40*	*40—45*	*45—50*	*50—55*	*55—60*	*60—65*	*65—70*	*70—75*	*75—80*	*90* —	Totals
0— 5	4	5	2	4	4	1	2	2	1	1	2	1	—	1	30
5—10	—	4	—	1	—	—	2	1	—	1	—	—	—	—	9
10—15	—	—	1	1	2	—	1	1	—	—	—	—	—	—	6
15—20	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
20—25	—	—	—	1	—	1	—	—	—	—	1	—	—	—	3
25—30	—	—	—	—	—	1	—	1	—	—	—	—	—	—	2
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
40—45	—	—	—	—	—	—	—	1	—	—	—	—	—	—	1
Totals	4	9	3	7	6	3	5	6	1	2	3	1	—	1	51

where persons have had a second attack of smallpox between the years 1887 and 1902, and of these fifty-one it is seen at once that thirty suffered from their first attack of smallpox below the age of five years, nine between the age of five and ten years, leaving a total of only twelve who had their first attack of smallpox above this age. This would seem to show that the protection afforded by an attack of smallpox in childhood is much less complete than that afforded by an attack after ten years. A study of the figures in the table seems to show that this is not due simply to the natural lessening in numbers which occurs in the population at each age period from childhood onwards. A certain amount of support is lent by this to the suggestion advanced earlier in this paper that vaccination performed in early adult life afforded a longer period of protection than when performed in infancy, and in both instances it may be surmised that as the natural susceptibility to smallpox increases from birth onwards till about twelve years there may be a greater loss of acquired immunity during the same period of life than is likely to occur when the natural protection against smallpox has become more definitely established. With regard to the protection which an attack of smallpox provides against death even less can be said. Of these fifty-one cases seven died. Five of these deaths, however, occurred in one epidemic out of twenty-three cases, and, although one of these five died from apoplexy, yet even four deaths out of twenty-three cases represents a mortality so much in

excess of what might be expected as to make it probable that these figures are not sufficiently large to be taken as trustworthy. The actual protection, however, which one attack of smallpox affords against a second is much larger than that conferred by vaccination; this protection, judging from the Sheffield census, is very high, the correlation coefficient being ·6, and this high correlation of protection against attack suggests the probability of some error in the death rate as given above.

The protection given by revaccination is still higher than that given by a previous attack of smallpox and by recent revaccination practically absolute. Of the 400,000 persons revaccinated in Glasgow in 1901 six were admitted during the epidemic of 1904; three of these stated that there had been no local reaction, they were therefore not effectively revaccinated; one stated that there had been a local reaction, which, however, left no scar. In the other two the condition of the arm indicated successful revaccination. That is out of 400,000 persons three at the most were affected with smallpox after a lapse of three years, while of the other 250,000 inhabitants of Glasgow more than 800 succumbed. In the statistics published in the London epidemic of 1902 the mean period which has elapsed between revaccination and the attack of smallpox (23·9 years) falls considerably short of the mean age of those attacked by smallpox in the same epidemic (28·6 years) with the protection alone of infantile vaccination. These persons, however, must represent a more susceptible class, for, judging from the Sheffield epidemic, the correlation between the revaccinated who escape and those who were attacked and the like classes of the vaccinated is very considerably in favour of the former.

TABLE XVI.

Table of Revaccinated Persons Attacked by Smallpox. London, 1902.

Age at Attack.

Age at Revaccination.	10—15	15—20	20—25	25—30	30—35	35—40	40—45	45—50	50—55	55—60	60—65	65—70	70—75	Totals
0— 5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5—10	1	—	—	1	1	1	—	4	1	—	—	—	—	9
10—15	1	—	2	5	2	4	7	5	—	—	1	—	—	27
15—20	—	—	1	—	6	2	10	3	2	2	—	1	—	27
20—25	—	—	—	—	1	2	5	1	2	—	—	1	—	12
25—30	—	—	—	—	1	—	1	2	—	1	—	—	—	5
30—35	—	—	—	—	—	—	1	3	2	—	—	1	—	7
35—40	—	—	—	—	—	—	—	—	1	—	—	—	—	1
40—45	—	—	—	—	—	—	—	—	1	—	—	—	—	1
45—50	—	—	—	—	—	—	—	—	—	1	—	—	—	1
50—55	—	—	—	—	—	—	—	—	1	—	—	—	—	1
55—60	—	—	—	—	—	—	—	—	—	—	—	—	—	—
60—65	—	—	—	—	—	—	—	—	—	—	—	—	1	1
Totals	2	—	3	6	11	9	24	18	10	4	1	3	1	92

In the accompanying table those cases of revaccinated persons attacked by smallpox during the London epidemic of 1902 are given; the number is ninety-two in all, and among these two deaths occurred, in both of which the period of the latest vaccination had been at least twenty-four years previously. Few inferences can be drawn from this table; it is, however, to be noted that more than a third of the cases occur in persons revaccinated before the age of fifteen years, who, as far as the statistics of this hospital go, constitute a very much smaller proportion of the total revaccinated persons, indicating again that the operation performed at this age affords less permanent protection than when done later.

In conclusion, it is necessary to state that all the correlation coefficients in this paper were calculated by the short method given at the end of Prof. Pearson's memoir on the correlation among attributes not quantitatively measurable * by means of the formula

$$r = \sin\frac{\pi}{2}\left\{\frac{1}{\sqrt{1+\kappa^2}}\right\}, \text{ where } \kappa^2 = \frac{4abcdN^2}{(ad-bc)^2(a+d)(b+c)}.$$

If the values of r corresponding to $\log\kappa^2$ from $\bar{1}$ to 4 be first calculated, as is easily done with the help of a table of Gaussian addition logarithms, then it is a matter of only a few minutes to obtain a correlation coefficient. Prof. Pearson has found this formula true in most instances within the probable error; I myself have checked it with about twenty examples and only once found it give a result outside that error, so for the accuracy required in this paper it may be considered sufficient. When the numbers are in nearly all cases small the probable error is large, and little stress can be placed on the accuracy of an individual coefficient. A far better test in a subject like this, when very large numbers of coefficients have to be calculated, is their general concordance. In many cases they form part of a series which is *à priori* continuous, and consequently each affords a mutual check on the other of much greater value considering the number of cases involved than the calculation of the probable error. Considering the series tabulated in this paper, many instances will be seen where the coefficients fall so out of line with their immediate neighbours that it is evident that some large error is present.

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